REMARKS/ARGUMENTS

Applicants appreciate the Examiner's thoughtful comments in the July 26, 2006 Office Action ("Office Action"). With this Amendment, Applicants hope to place the claims in condition for allowance. Specifically, Applicants have made several amendments to independent claim 1. First, Applicants have amended the preamble of claim 1 to recite "diagnosing a mental disorder in a subject." Support for this Amendment may be found in the specification at, *e.g.*, paragraphs 65, 66, 89, 165, 202 and 216.

Second, Applicants have amended claim 1 to address the Examiner's rejection argument under 35 U.S.C. § 112, second paragraph. *See* Office Action at page 5. The Examiner stated that "typically, a polynucleotide is not 'encoded' by a nucleic acid per se." *Id.* Applicants respectively submit that messenger RNA molecules are typically referred to as encoded by genes by those skilled in the art. *See, e.g.*, U.S. Patent No. 6,841,367 at column 3, line 65.[1] In this regard, Applicants have amended claim 1 to more clearly refer to the *messenger RNA* encoded by the CAMIIK-alpha or TBR1 *genes* (represented by SEQ ID NOs 1 or 3, respectively), which are detected according to the claimed method. Support for this amendment may be found in the specification at, *e.g.*, paragraphs 18 and 208. The phrase "sample" has been replaced by "messenger RNA" in step (iii) of claim 1 to avoid a lack of antecedent basis.

Third, Applicants have amended claim 1 to remove the phrase "or is predisposed for." None of the foregoing amendments add new matter.

Finally, Applicants wish to remind the Examiner of their Species Election, dated September 30, 2005, in response to a Restriction Requirement mailed August 30, 2005. Specifically, Applicants elected the invention of Group I and three species: SEQ ID NO:3, nucleic acid (reagent), and bipolar disease. Applicants have amended claim 11 and added new dependent claim 52 to limit these claims to the elected species (original claim 3 is already limited the use of a "nucleic acid reagent"). Both of these claims (*i.e.*, amended claim 11 and new claim

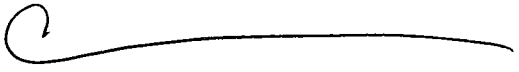
[1] The relevant passage reads as follows: "Any such polynucleotide includes but is not necessarily limited to nucleotide substitutions, deletions, additions, amino-terminal truncations and carboxy-terminal truncations such that these mutations *encode mRNA* ..." A copy of the relevant page of the '367 patent is attached as an Exhibit.

52) incorporate all of the limitations of the generic claim 1 and, therefore, no new matter is added.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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ties. These monoclonal antibodies also inhibit the growth of typically less well vascularized human colon cancers in athymic mice and decrease the number of tumors arising from inoculated cells. Viral expression of a VEGF-binding construct of Flk-1, the mouse KDR receptor homologue, truncated to eliminate the cytoplasmic tyrosine kinase domains but retaining a membrane anchor, virtually abolishes the growth of a transplantable glioblastoma in mice presumably by the dominant negative mechanism of heterodimer formation with membrane-spanning endothelial cell VEGF receptors. Embryonic stem cells, which normally grow as solid tumors in nude mice, do not produce detectable tumors if both VEGF alleles are knocked out. Taken together, these data indicate the role of VEGF in the growth of solid tumors. KDR and Flt-1 are implicated in pathological neoangiogenesis, and inhibitors of these receptors are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, various forms of cancer as well as forms of inflammation such as rheumatoid arthritis, psoriasis, contact dermatitis and hypersensitivity reaction.

Terman et al. (1991, *Oncogene* 6: 1677–1683; 1992, *Biochem. Biophys. Res. Commun.* 187: 1579–1586) disclose a full-length cDNA encoding a form of KDR. However, the Terman et al. disclosures do not identify a novel, optimal nucleic acid fragment encoding the human form of the receptor type tyrosine kinase gene, KDR. It will be advantageous to identify and isolate a human cDNA sequence encoding an optimized form of human KDR. A nucleic acid molecule expressing the human KDR protein will be useful in screening for compounds acting as a modulator of the protein kinase domain of this protein. Such a compound or compounds will be useful in modulating the mitogenic signal of VEGF and VEGF-related proteins on vascular endothelial cells. The KDR nucleic acid sequence may be also useful for gene therapy encoding a portion of the KDR protein that would contain functional ligand binding and membrane anchoring moieties but not tyrosine linase activity. Either all or a portion of the KDR protein is also useful to screen for VEGF antagonists. The KDR nucleic acid sequence can be transfected into cells for analysis of function in the absence of Flt-1. The KDR protein is also useful for x-ray structure analysis in the presence or absence of ligand and/or inhibitors. The present invention addresses and meets these needs by disclosing an isolated nucleic acid fragment which expresses a form of human KDR which is shown by computer modeling to be predictive of higher activity and functionality than the previously disclosed KDR.

SUMMARY OF THE INVENTION

The present invention relates to an isolated nucleic acid molecule (polynucleotide) which encodes a novel human receptor type tyrosine kinase gene, KDR. This specification discloses a novel, optimized DNA molecule which encodes, KDR, a receptor tyrosine kinase expressed on human endothelial cells.

The present invention also relates to biologically active fragments or mutants of SEQ ID NO:1 which encodes mRNA expressing a novel human receptor type tyrosine kinase gene, KDR. Any such biologically active fragment and/or mutant will encode either a protein or protein fragment comprising at least an intracellular or extracelluar kinase domain similar to that of the human KDR protein as set forth in SEQ ID NO:2. Any such polynucleotide includes but is not necessarily limited to nucleotide substitutions, deletions, additions, amino-terminal truncations and carboxy-terminal truncations such that these mutations encode mRNA which express a protein or protein fragment of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for KDR function.

The isolated nucleic acid molecule of the present invention may include a deoxyribonucleic acid molecule (DNA), such as genomic DNA and complementary DNA (cDNA), which may be single (coding or noncoding strand) or double stranded, as well as synthetic DNA, such as a synthesized, single stranded polynucleotide. The isolated nucleic acid molecule of the present invention may also include a ribonucleic acid molecule (RNA).

The present invention also relates to recombinant vectors and recombinant hosts, both prokaryotic and eukaryotic, which contain the substantially purified nucleic acid molecules disclosed throughout this specification.

The present invention also relates to subcellular membrane fractions of the recombinant host cells (both prokaryotic and eukaryotic as well as both stably and transiently transformed cells) comprising the nucleic acids of the present invention. These subcellular membrane fractions will comprise either wild-type or human mutant forms of KDR at levels substantially above wild-type levels and hence will be useful in various assays described throughout this specification.

A preferred aspect of the present invention is disclosed in FIG. 1A and FIG. 1B and SEQ ID NO:1, a human cDNA encoding a novel receptor type tyrosine kinase gene, KDR.

The present invention also relates to a substantially purified form of the receptor type tyrosine kinase gene, KDR which is disclosed in FIG. 2 and as set forth in SEQ ID NO:2.

The present invention also relates to biologically active fragments and/or mutants of the KDR protein as initially set forth as SEQ ID NO:2, including but not necessarily limited to amino acid substitutions, deletions, additions, amino terminal truncations and carboxy-terminal truncations such that these mutations provide for proteins or protein fragments of diagnostic, therapeutic or prophylactic use and would be useful for screening for agonists and/or antagonists for KDR function.

A preferred aspect of the present invention is disclosed in FIG. 2 and is set forth as SEQ ID NO:2, the amino acid sequence of the novel receptor type tyrosine kinase gene, KDR.

The present invention also relates to polyclonal and monoclonal antibodies raised in response to either the human form of KDR disclosed herein, or a biologically active fragment thereof.

The present invention also relates to isolated nucleic acid molecules which are fusion constructions expressing fusion proteins useful in assays to identify compounds which modulate wild-type human KDR activity. A preferred aspect of this portion of the invention includes, but is not limited to, glutathione S-transferase (GST)-KDR fusion constructs. These fusion constructs include, but are not limited to, either the intracellular tyrosine kinase domain of human KDR as an in-frame fusion at the carboxy terminus of the GST gene or the extracellular ligand binding domain fused to an immunoglobulin gene by methods known to one of ordinary skill in the art. Soluble recombinant GST-kinase domain fusion proteins may be expressed in various expression systems, including *Spodoptera frugiperda* (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).